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FILE 'USPATFULL' ENTERED AT 17:58:24 ON 13 JUN 2003

                E LAVELLE E C/IN
L1            1 S E4
                E OHAGAN D/IN
                E O HAGAN D/IN
L2           12 S E5
L3            4 S L2 AND (INTRANASAL?)
L4            1 S L3 AND BIOADHESIVE
L5            3 S L3 NOT L4
L6        63980 S ADJUVANT?
L7         3617 S L6 AND (PLANT LECTIN OR LECTIN)
L8         3484 S L7 AND (ML? OR MISTLETOE LECTIN OR WGA OR WHEAT GERM AGGLUTIN
L9          184 S L8 AND LECTIN/CLM
L10          36 S L9 AND (ADJUVANT/CLM)
L11           6 S L10 AND (ML?/CLM OR MISTLTOE/CLM OR WGA/CLM OR WHEAT/CLM OR U
L12           0 S L9 AND MISTLETOE/CLM
L13          23 S L9 AND WHEAT/CLM
L14          21 S L13 NOT L11

FILE 'MEDLINE' ENTERED AT 18:09:13 ON 13 JUN 2003

L15        3643 S PLANT LECTIN?
L16          80 S L15 AND ADJUVANT?

FILE 'USPATFULL' ENTERED AT 18:18:50 ON 13 JUN 2003

L17           0 S US4470967
L18           1 S US4470967/PN
L19       12010 S LECTIN?
L20        4301 S L19 AND ADJUVANT?
L21        3333 S L20 AND (IMMUNIZ?)
L22         798 S L21 AND MUCOSAL
L23          42 S L22 AND PY=1998
L24          47 S L22 AND PY=1999

FILE 'MEDLINE' ENTERED AT 18:27:10 ON 13 JUN 2003

L25       68843 S ADJUVANT?
L26        2159 S L25 AND (PROBLEM? OR PITFALL? OR LIMITATION?)
L27           5 S L26 AND LECTIN?
L28         158 S L26 AND PY=1999
L29          12 S L28 AND ADJUVANT/TI
L30         287 S L26 AND ADJUVANT?/TI
L31          22 S L30 AND PY=2000
L32          41 S L30 AND VACCIN?
L33         356 S MUCOSAL ADJUVANT?
L34           2 S L33 AND LECTIN?
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424/88

L16 ANSWER 60 OF 80 MEDLINE
95323976 Document Number: 95323976. PubMed ID: 7600586. Bioadhesion technologies for the delivery of peptide and protein drugs to the gastrointestinal tract. Lehr C M. (Department of Biopharmaceutics and Pharmaceutical Technology, Universitat des Saarlandes, Germany.) CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, (1994) 11 (2-3) 119-60. Ref: 191. Journal code: 8511159. ISSN: 0743-4863. Pub. country: United States. Language: English.

AB For the efficient delivery of peptides, proteins, and other biopharmaceuticals by nonparenteral routes, in particular via the gastrointestinal, or GI, tract, novel concepts are needed to overcome significant enzymatic and diffusional barriers. In this context, bioadhesion technologies offer some new perspectives. The original idea of oral bioadhesive drug delivery systems was to prolong and/or to intensify the contact between controlled-release dosage forms and the stomach or gut mucosa. However, the results obtained during the past decade using existing pharmaceutical polymers for such purposes were rather disappointing. The encountered difficulties were mainly related to the physiological peculiarities of GI mucus. Nevertheless, research in this area has also shed new light on the potential of mucoadhesive polymers. First, one important class of mucoadhesive polymers, poly(acrylic acid), could be identified as a potent inhibitor of proteolytic enzymes. Second, there is increasing evidence that the interaction between various types of bio(muco)adhesive polymers and epithelial cells has direct influence on the permeability of mucosal epithelia. Rather than being just adhesives, mucoadhesive polymers may therefore be considered as a novel class of multifunctional macromolecules with a number of desirable properties for their use as biologically active drug delivery adjuvants. To overcome the problems related to GI mucus and to allow longer lasting fixation within the GI lumen, bioadhesion probably may be better achieved using specific bioadhesive molecules. Ideally, these bind to surface structures of the epithelial cells themselves rather than to mucus by receptor-ligand-like interactions. Such compounds possibly can be found in the future among plant lectins, novel synthetic polymers, and bacterial or viral adhesion/invasion factors. Apart from the plain fixation of drug carriers within the GI lumen, direct bioadhesive contact to the apical cell membrane possibly can be used to induce active transport processes by membrane-derived vesicles (endo- and transcytosis). The nonspecific interaction between epithelia and some mucoadhesive polymers induces a temporary loosening of the tight intercellular junctions, which is suitable for the rapid absorption of smaller peptide drugs along the paracellular pathway. In contrast, specific endo- and transcytosis may ultimately allow the selectively enhanced transport of very large bioactive molecules (polypeptides, polysaccharides, or polynucleotides) or drug carriers across tight clusters of polarized epi- or endothelial cells, whereas the formidable barrier function of such tissues against all other solutes remains intact.

L18 ANSWER 1 OF 1 USPATFULL
84:51192 Lectin-containing anti-viral vaccines for domestic animals and method of preparation.
Gough, Patricia M., Ames, IA, United States
Platt, Kenneth B., Ames, IA, United States
Iowa State University Research Foundation, Ames, IA, United States (U.S. corporation)
US 4470967 19840911 <--
APPLICATION: US 1982-432820 19821005 (6)
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Anti-viral vaccines for domestic animals are prepared from glycoprotein envelope whole virus or antigenic glycoprotein obtained therefrom by complexing the glycoprotein antigenic agent with a lectin, which is preferably a mitogenic lectin. The recovery of the immunizing agent from an aqueous solution or suspension is facilitated since the lectin-glycoprotein complex is readily recoverable. The mitogenic lectin administered in the vaccine with the glycoprotein antigen can enhance the anamnestic response, in effect, acting as an adjuvant.

CLM What is claimed is:

1. A veterinary vaccine in parenterally injectable dose form, comprising an effective immunizing dose amount of viral antigen immunizing agent selected from the class consisting of (i) whole viruses having envelopes containing at least one glycoprotein or (ii) the separated viral envelope glycoprotein obtained from such viruses, and a mitogenic lectin complexed with the glycoprotein of said immunizing agent, said complexed lectin providing binding sites available for lymphocytes, and said vaccine containing at least from 0.01 to 0.1 milligrams (mg) of said mitogenic lectin per milligram (mg) of glycoprotein.

2. The vaccine of claim 1 in which said immunizing agent comprises transmissible gastroenteritis (TGE) virus or separated glycoprotein obtained therefrom.

3. The vaccine of claim 2 in which said immunizing agent comprises separated TGE envelope glycoprotein.

4. The vaccine of claim 1 in which said immunizing agent comprises pseudorabies (PR) virus or glycoprotein obtained therefrom.

5. The vaccine of claim 4 in which said immunizing agent comprises separated pseudorabies .degree.PR1 envelope glycoprotein.

6. The vaccines of claims 1 to 5 in which said lectin is lentil bean lectin.

7. The method of preparing and administering a veterinary vaccine, comprising: (a) preparing an aqueous solution or suspension of a viral antigen immunizing agent selected from the class consisting of (i) whole viruses having envelopes containing at least one glycoprotein or (ii) the separated viral envelope glycoprotein obtained from such viruses; (b) contacting said immunizing agent in said aqueous solution or suspension with a lectin reagent capable of complexing with the glycoprotein of said immunizing agent, said lectin reagent being a mitogenic lectin and a sufficient amount of said lectin reagent being employed to form a readily separable complex from said immunizing agent; (c) recovering the thus-formed lectin-glycoprotein complex of the immunizing agent; (d) preparing a parenterally injectable vaccine from said immunizing agent without separating the lectin therefrom, the lectin in said complex having binding sites available for lymphocytes; and (e) administering an effective immunizing dose amount of said vaccine by parenteral injection to an animal capable of being immunized by said immunizing agent.

8. The method of claim 7 in which said lectin is in water-soluble form when complexed with said immunizing agent.

9. The method of claim 7 in which said lectin when complexed with said immunizing agent is immobilized on a particulate support material.

10. The method of claims 7, 8, or 9 in which said lectin is lentil bean lectin.

11. The method of claims 7, 8, or 9 in which said immunizing agent comprises transmissible gastroenteritis virus or separated glycoprotein obtained therefrom.

12. The method of claims 7, 8, or 9 in which said immunizing agent comprises pseudorabies (PR) virus or separated glycoprotein obtained therefrom.

13. The method of claim 7 in which said immunizing agent is separated viral envelope glycoprotein, and both said glycoprotein and said lectin are dissolved in said aqueous solution for said complexing reaction.

14. The method of claim 13 in which said glycoprotein is obtained from transmissible gastroenteritis (TGE) virus, and said lectin is lentil bean lectin.

15. The method of claim 13 in which said glycoprotein is obtained from pseudorabies (PR) virus, and said lectin is lentil bean lectin.

16. A veterinary vaccine in parenterally injectable dose form, comprising an effective immunizing dose amount of viral antigen immunizing agent consisting of viral envelope glycoprotein separated from a virus having an envelope containing at least one glycoprotein, and a mitogenic lectin complexed with said immunizing agent, said complexed lectin providing binding sites available for lymphocytes, and said vaccine containing at least from 0.01 to 0.1 milligrams (mg) of said mitogenic lectin per milligram (mg) of glycoprotein.

17. The method of preparing and administering a veterinary vaccine comprising: (a) preparing an aqueous solution of a viral antigen immunizing agent consisting of separated viral envelope glycoprotein obtained from a virus having an envelope containing at least one glycoprotein; (b) contacting said immunizing agent in said aqueous solution with a lectin reagent capable of complexing with the glycoprotein of said immunizing agent, said lectin reagent being a mitogenic lectin and a sufficient amount of said lectin reagent being employed to form a readily separable complex from said immunizing agent; (c) recovering the thus-formed lectin-glycoprotein complex; (d) preparing a parenterally injectable vaccine from said immunizing agent without separating the lectin therefrom the lectin in said complex having binding sites available for lymphocytes; and (e) administering an effective immunizing dose amount of said vaccine by parenteral injecting to an animal capable of being immunized by said immunizing agent.

L23 ANSWER 19 OF 42 USPATFULL
1998:118870 Method for delivering bioactive agents into and through the mucosally associated lymphoid tissues and controlling their release.
Tice, Thomas R., Birmingham, AL, United States
Gilley, Richard M., Birmingham, AL, United States
Eldridge, John H., Birmingham, AL, United States
Staas, Jay K., Birmingham, AL, United States
Southern Research Institute, Birmingham, AL, United States (U.S. corporation)The UAB Research Foundation, Birmingham, AL, United States (U.S. corporation)
US 5814344 19980929 <--
APPLICATION: US 4692187 19950606 (8)
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method, and compositions for use therein capable, of delivering a bioactive agent to an animal entailing the steps of encapsulating effective amounts of the agent in a biocompatible excipient to form microcapsules having a size less than approximately ten micrometers and administering effective amounts of the microcapsules to the animal. A pulsatile response is obtained, as well as mucosal and systemic immunity.

L27 ANSWER 1 OF 5 MEDLINE
95323976 Document Number: 95323976. PubMed ID: 7600586. Bioadhesion technologies for the delivery of peptide and protein drugs to the gastrointestinal tract. Lehr C M. (Department of Biopharmaceutics and Pharmaceutical Technology, Universitat des Saarlandes, Germany.) CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, (1994) 11 (2-3) 119-60. Ref: 191. Journal code: 8511159. ISSN: 0743-4863. Pub. country: United States. Language: English.

AB For the efficient delivery of peptides, proteins, and other biopharmaceuticals by nonparenteral routes, in particular via the gastrointestinal, or GI, tract, novel concepts are needed to overcome significant enzymatic and diffusional barriers. In this context, bioadhesion technologies offer some new perspectives. The original idea of oral bioadhesive drug delivery systems was to prolong and/or to intensify the contact between controlled-release dosage forms and the stomach or gut mucosa. However, the results obtained during the past decade using existing pharmaceutical polymers for such purposes were rather disappointing. The encountered difficulties were mainly related to the physiological peculiarities of GI mucus. Nevertheless, research in this area has also shed new light on the potential of mucoadhesive polymers. First, one important class of mucoadhesive polymers, poly(acrylic acid), could be identified as a potent inhibitor of proteolytic enzymes. Second, there is increasing evidence that the interaction between various types of bio(muco)adhesive polymers and epithelial cells has direct influence on the permeability of mucosal epithelia. Rather than being just adhesives, mucoadhesive polymers may therefore be considered as a novel class of multifunctional macromolecules with a number of desirable properties for their use as biologically active drug delivery adjuvants. To overcome the problems related to GI mucus and to allow longer lasting fixation within the GI lumen, bioadhesion probably may be better achieved using specific bioadhesive molecules. Ideally, these bind to surface structures of the epithelial cells themselves rather than to mucus by receptor-ligand-like interactions. Such compounds possibly can be found in the future among plant lectins, novel synthetic polymers, and bacterial or viral adhesion/invasion factors. Apart from the plain fixation of drug carriers within the GI lumen, direct bioadhesive contact to the apical cell membrane possibly can be used to induce active transport processes by membrane-derived vesicles (endo- and transcytosis). The nonspecific interaction between epithelia and some mucoadhesive polymers induces a temporary loosening of the tight intercellular junctions, which is suitable for the rapid absorption of smaller peptide drugs along the paracellular pathway. In contrast, specific endo- and transcytosis may ultimately allow the selectively enhanced transport of very large bioactive molecules (polypeptides, polysaccharides, or polynucleotides) or drug carriers across tight clusters of polarized epi- or endothelial cells, whereas the formidable barrier function of such tissues against all other solutes remains intact.

L32 ANSWER 2 OF 41 MEDLINE

2002315892 Document Number: 22053721. PubMed ID: 12057597. A dilemma for mucosal vaccination: efficacy versus toxicity using enterotoxin-based adjuvants. Fujihashi Kohtaro; Koga Toshiya; van Ginkel Frederik W; Hagiwara Yukari; McGhee Jerry R. (Department of Microbiology, BBRB Room 716, Immunobiology Vaccine Center, University of Alabama at Birmingham, Medical Center, 35294-2170, USA.. kohtarof@uab.edu) . VACCINE, (2002 Jun 7) 20 (19-20) 2431-8. Ref: 61. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB In the development of mucosal vaccines, cholera toxin (CT) has been shown to be an effective adjuvant and to induce both mucosal and systemic immune responses via a Th2 cell-dependent pathway. However, a major concern for use of mucosal adjuvants such as CT is that this molecule is not suitable for use in humans because of its innate toxicity. Recent vaccine development efforts have emphasized nasal application of antigen and CT for the induction of mucosal IgA responses. When we examined potential toxicity of CT for the central nervous system (CNS), both CT and CT-B accumulated in the olfactory nerves/epithelium and olfactory bulbs of mice when given by the nasal route. The development of effective mucosal vaccines for the elderly is also an important issue; however, only limited information is available. When mucosal adjuvanticity of CT was evaluated in aged mice, an early immune dysregulation was evident in the mucosal immune system. The present review discusses these potential problems for effective mucosal vaccine development.

L32 ANSWER 7 OF 41 MEDLINE

2001541659 Document Number: 21472816. PubMed ID: 11587808. What are the limits of adjuvanticity?. Del Giudice G; Podda A; Rappuoli R. (IRIS Research Center, Chiron SpA, Via Fiorentina 1, 53100, Siena, Italy.) VACCINE, (2001 Oct 15) 20 Suppl 1 S38-41. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB Vaccines developed traditionally following empirical approaches have often limited problems of immunogenicity, probably due to the low level of purity of the active component(s) they contain. The application of new technologies to vaccine development is leading to the production of purer (e.g. recombinant) antigens which, however, tend to have a poorer immunogenicity as compared to vaccines of the previous generation. The search for new vaccine adjuvants involves issues related to their potential limits. Since the introduction of aluminium salts as vaccine adjuvants more than 70 years ago, **only one adjuvant has been licensed for human use. The development of some of these new vaccine adjuvants has been hampered by their inacceptable reactogenicity.** In addition, **some adjuvants work strongly with some antigens but not with others, thus, limiting their potentially widespread use.** The need to deliver vaccines via alternative routes of administration (e.g. the mucosal routes) in order to enhance their efficacy and compliance has set new requirements in basic and applied research to evaluate their efficacy and safety. Cholera toxin (CT) and labile enterotoxin (LT) mutants given along with intranasal or oral vaccines are strong candidates as mucosal adjuvants . Their potential reactogenicity is still matter of discussions, although available data support the notion that the effects due to their binding to the cells and those due to the enzymatic activity can be kept separated. Finally, adjuvanticity is more often evaluated in terms of antigen-specific antibody titers induced after parenteral immunization. It is known that, in many instances, **antigen-specific antibody titers do**

not correlate with protection. In addition, very little is known on parameters of cell-mediated immunity which could be considered as surrogates of protection. Tailoring of new adjuvants for the development of vaccines with improved immunogenicity/efficacy and reduced reactogenicity will represent one of the major challenges of the ongoing vaccine-oriented research.

L32 ANSWER 18 OF 41 MEDLINE
1998214879 Document Number: 98214879. PubMed ID: 9554260. Biodegradable polymer microspheres as vaccine adjuvants and delivery systems. Gupta R K; Chang A C; Siber G R. (Massachusetts Public Health Biologic Laboratories, State Laboratory Institute, Boston, USA.) DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (1998) 92 63-78. Ref: 84. Journal code: 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.

AB Though vaccination has been the most cost-effective way of controlling infectious diseases, the logistics of delivering at least two to three doses of conventional vaccines for primary immunization to achieve protection are difficult and compliance is frequently inadequate, particularly in developing countries. In recent years biodegradable polymer microspheres have received much attention for the purposes of controlled release of antigens, (i) to reduce the number of doses needed for primary immunization to as few as a single dose and (ii) to target an antigen to microfold cells on mucosal surfaces after oral administration or to antigen-presenting cells after parenteral inoculations. A variety of vaccine antigens have been encapsulated in microspheres usually composed of poly (lactic/glycolic) acid (PLGA). Based on the size of the microspheres, molecular weight of polymer and ratio of lactic to glycolic acid in the polymer, the antigen may be targeted to various cells of the immune system or it may form a depot at the site of injection, allowing the slow release of the antigen for extended periods. Additionally, another adjuvant may be incorporated inside microspheres together with the antigen, further enhancing or modulating the immune response to the desired type. The major problems in developing controlled-release vaccines include instability of vaccine antigens during micro-encapsulation, storage and subsequent hydration. We encapsulated tetanus toxoid (TT) and Haemophilus influenzae type b capsular polysaccharide conjugated to TT (Hib-T) inside PLGA microspheres and evaluated the antibody levels in mice. A single injection of these micro-encapsulated vaccines elicited high antibody levels which persisted for several months. The antibody levels were similar or superior to those elicited by conventional formulations of AlPO4-adsorbed TT or soluble Hib-T conjugate vaccine.

L32 ANSWER 22 OF 41 MEDLINE
96155133 Document Number: 96155133. PubMed ID: 8585280. Adjuvants for human vaccines--current status, problems and future prospects. Gupta R K; Siber G R. (Massachusetts Public Health Biologic Laboratories, State Laboratory Institute, Boston 02130, USA.) VACCINE, (1995 Oct) 13 (14) 1263-76. Ref: 123. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Adjuvants help antigen to elicit an early, high and long-lasting immune response with less antigen, thus saving on vaccine production costs. In recent years, adjuvants received much attention because of the development of purified, subunit and synthetic vaccines which are poor immunogens and require adjuvants to evoke the immune response. With the use of adjuvants immune response can be selectively modulated to major histocompatibility complex

(MHC) class I or MHC class II and Th1 or Th2 type, which is very important for protection against diseases caused by intracellular pathogens such as viruses, parasites and bacteria (Mycobacterium). **A number of problems are encountered in the development and use of adjuvants for human vaccines. The biggest issue with the use of adjuvants for human vaccines, particularly routine childhood vaccines, is the toxicity and adverse side-effects of most of the adjuvant formulations.** At present the choice of adjuvants for human vaccination reflects a compromise between a requirement for adjuvanticity and an acceptable low level of side-effects. **Other problems with the development of adjuvants include restricted adjuvanticity of certain formulations to a few antigens, use of aluminum adjuvants as reference adjuvant preparations under suboptimal conditions, non-availability of reliable animal models, use of non-standard assays and biological differences between animal models and humans leading to the failure of promising formulations to show adjuvanticity in clinical trials.** The most common adjuvants for human use today are still aluminum hydroxide and aluminum phosphate, although calcium phosphate and oil emulsions also have some use in human vaccinations. During the last 15 years much progress has been made on development, isolation and chemical synthesis of alternative adjuvants such as derivatives of muramyl dipeptide, monophosphoryl lipid A, liposomes, QS21, MF-59 and immunostimulating complexes (ISCOMS). Other areas in adjuvant research which have received much attention are the controlled release of vaccine antigens using biodegradable polymer microspheres and reciprocal enhanced immunogenicity of protein-polysaccharide conjugates. Biodegradable polymer microspheres are being evaluated for targeting antigens on mucosal surfaces and for controlled release of vaccines with an aim to reduce the number of doses required for primary immunization. Reciprocal enhanced immunogenicity of protein-polysaccharide conjugates will be useful for the development of combination vaccines.